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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/813,829	03/06/97	HOGAN	B 16016.0005

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EXAMINER	
WOITACH, J	
ART UNIT	PAPER NUMBER
1632	19

DATE MAILED: 06/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Offic Action Summary	Application No.	Applicant(s)	
	08/813,829	HOGAN, BRIGID L. M.	
	Examiner	Art Unit	
	Joseph Woitach	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 February 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☒ The proposed drawing correction filed on *03-06-97* is: a)☐ approved b)☒ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Please note that the Examiner of record and art unit has changed. The Examiner of record is now **Joseph Woitach** and the group art unit is now **1632**.

A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on February 28, 2001, paper number 17, has been entered.

The amendment filed February 28, 2001, paper number 18, has been received and entered. Claims 1 and 4 have been amended. Claims 1-4 are pending and currently under examination.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

Applicants summarize the disclosure of application 07/958,563, now patent US Patent 5,453,357, and argue that it is inconsistent that the office has found the disclosure of '563 fully enabled for and allowed claims to a method of making pluripotential embryonic stem cells, however maintain that '563 fails to enable the product of an isolated non-murine pluripotential cell as claimed in the instant application. Applicants state that the legal standard for enablement is whether the specification is sufficient to enable a person skilled in the art to make or use the invention, and cite 35 USC 112 first paragraph and *Atmel Corp. v. Information Storage Devices, Inc.* 53, USPQ 2d. 1225 (Fed. Cir. 1999) in support of their argument. Further, Applicants argue that the specification must teach the skilled artisan how to make and use the invention without undue experimentation (citing *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997), and that a considerable amount of experimentation is permissible so long as it is merely routine or so long as the 'specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice *a desired embodiment of the invention claimed*' (emphasis added)(citing *Ex parte Jackson*, 217, USPQ 804, 807 (1982). See Applicants amendment pages 3-5. Applicants arguments have been fully considered but not found persuasive.

The office maintains the refusal to grant priority for two reasons; first, the method of making a pluripotential embryonic stem cell claimed in '357 does not necessarily result in the product of the pluripotential cell claimed in '829 ; and secondly, even if one could use the method

of '357 to obtain the instantly claimed pluripotential cell, there is no clear teaching nor indication that the methods in '357 will result in the characteristics of the cell recited instant claims.

The claims of '357 are drawn to a method of making pluripotential embryonic stem cells and it is noted that no specific characteristics of the a pluripotential embryonic stem cell are recited in the claim (see claims 1-14 of patent 5,435,357). The instant claims of '829 are drawn to a pluripotential cell, a possibly related but different cell than a pluripotential embryonic stem cell. Further, the claims of '829 recite specific characteristics of; maintained on a feeder layers for at least 20 passages; give rise to embroid bodies; has potency characteristics; and as newly amended, include having a normal karyotype. Review of the prosecution history of the instant application indicates that the office originally maintained a 112 first paragraph rejection over a non-murine pluripotential embryonic stem cell because the specification failed to provide the necessary guidance to overcome the unpredictability of creating an embryonic stem cell from any other animal besides the mouse. The claims were amended to recite a pluripotential cell, and the rejection was withdrawn, the Examiner conceding that a pluripotential cell were well known in the art and could be obtained given the guidance of the instant specification. However, it is maintained that there is not a clear nexus between practicing the methods of '357 and obtaining a pluripotential cell with the recited characteristics in the instant claims. The instant specification and the specification of '357 supports this assertion where it teaches '[W]hile the ES cell are non-mouse, it is possible that the ES cells produced by the combination of FGF, LIF and SF physically differ from existing established murine ES cell. Thus, murine ES cells produced by the addition of

FGF, LIF and SF are also contemplated" (column 4; lines 17-21). Thus, Applicants own specification clearly indicates that the characteristics of a cell derived with the claimed methods could not be predicted, and may actually be different from other ES cells or pluripotential cells which have already been derived, and thus does not support isolation of a cell with a desired embodiment of the invention claimed (*Ex parte Jackson*). In addition, the claims now recite 'the characteristics of the cell include having a normal karyotype' (claims 1 and 4). This characteristic is the basis of a new 35 USC 112 first paragraph rejection (see below). With respect to priority, the specification teaches that only one cell after 20 passages was karyotyped (3/20) and that 'there was a significant proportion of trisomic cells' (see '357, column 8; lines 17-20). Further, of the two lines passaged only fourteen times, one was normal (1/14), but the second had significant proportion of trisomic cells (2/14). Given these results and the unpredictability of the art of generating pluripotential cells there is no clear teaching in '357 that would lead one of skill in the art to predict that the claimed methods of '357 would result in the cells with a normal karyotype as recited in the instant claims of '829. Therefore, for the reasons above and of record, priority to '357 is not granted for application '829.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to

make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a non-murine mammalian pluripotential cell, does not reasonably provide enablement for non-murine mammalian pluripotential cell wherein the characteristics of the cell includes having a normal karyotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The nature of the claimed invention a non-murine mammalian pluripotential cell wherein one of the characteristics of the cell includes having a normal karyotype. As noted previously, the art of isolating pluripotential ES-like cells is not well established and highly unpredictable (paper number 8; pages 2-4). The Examiner concedes that non-murine pluripotential cells can be generated with the methods taught in the instant specification, the methods previously taught to produce these cells differ from those taught in the instant specification. As taught in the instant specification "it is possible that the ES cells produced by the combination of FGF, LIF and SF physically differ from existing established murine ES cell. Thus, murine ES cells produced by the addition of FGF, LIF and SF are also contemplated" (column 4; lines 17-21). Applicants specification indicates that the characteristics of a cell derived with the claimed methods can not be predicted, and may actually be different from other ES cells or pluripotential cells which have already been derived. In addition, Piedrahita *et al.* teach that porcine and ovine embryos respond differently to the same treatments and that conditions that allowed the production of porcine ES-

like cells did not allow development of ovine ES-like cells (page 886; Table 1 and page 888). Further, as discussed in Cruz *et al.*, the embryonic development of different mammals varies, and thus, depending on the time and location of the isolation of the cell from the embryo, the nature of a cell isolated from said embryo can also vary. Therefore, methods to isolate a pluripotential cell from one mammal cannot be extrapolated for use in another mammal to obtain a similar cell from a second species of mammal. Further, as evidenced by the art and noted in the specification, the phenotype of pluripotential cell isolated by different methods may result in a phenotypically different cell.

With respect to achieving a cell with a normal karyotype, the only working example provided in the instant specification teaches the generation of a murine ES-like cell that only one cell after 20 passages was karyotyped (3/20) and that 'there was a significant proportion of trisomic cells' (see '357, column 8; lines 17-20). Further, of two lines passaged only fourteen times, one was normal (1/14), but the second had significant proportion of trisomic cells (2/14). Given the specific results taught in the specification and the unpredictability of the art of generating pluripotential mammalian cells, there is no clear teaching supporting that the present methodology would predictably result in a pluripotential cell with a normal karyotype, in particular a cell which is passaged 20 times. Even if one were to concede that pluripotential murine cells with a normal karyotype could be isolated using the methods taught in the instant specification, in light of the unpredictability of the art in generating pluripotential cells, there is no

clear nexus that methods used successfully to generate a mouse cell with a normal karyotype can be used to generate pluripotential cells with a normal karyotype from other mammals.

In view of the lack of guidance, working examples, breadth of the claims, the level of skill in the art at the time the claimed invention was made, it would have required one of skill in the art undue experimentation to practice the invention as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically:

Claims 1 and 4 have been amended to recite "said cell has the potency characteristics of a cell derived from a primordial germ cell" (claim 1) and "said cell has [all] the [essential] potency characteristics of a cell derived from a primordial germ cell" (claim 4). Literal support for the term 'potency' is not found in the instant specification. Merriam Webster defines 'potency' as the quality or state of being potent, and defines 'potent' as rich in a characteristic constituent. The cell is neither defined by a specific capacity nor by specific characteristics constituents. As noted previously, the cell is defined by the process used to obtain the cell recited in steps (a) and (b) of the claim, and absent defining characteristics, the process must be a required limitation in the

claim (previous office action, paper number 12, page 3). The claims are vague, unclear and indefinite in defining the metes and bounds of the claims because the skilled artisan is not apprized as to what characteristics the cell has which endows potency to the cell. The claims have also been amended to recite "wherein the characteristics of the cell include having a normal karyotype", however this is just one additional characteristic of the cell which is not clearly associated in the specification with any 'potency characteristics'.

Claim 2 is vague and unclear in the recitation of 'having a mutation which renders a gene non-functional' because it is unclear what portion or function of the gene is rendered non-functional. A gene has many components such as promoters, enhancers, transcriptional start and stop sites. In addition, mutations can be introduced into the coding sequence of a gene which do not affect the gene *per se* and transcription of the gene is normal, however the gene produces a mRNA which does not encode a functional protein. It is unclear if the claim encompasses these types of mutations since the gene would still be considered functional, however the gene product, the transcribed polypeptide would not be functional.

Claim 3 is vague and unclear in the recitation of 'having an insertion of a functional gene' because it is not clear if the insertion is into the genome of the cell or simply inserted episomally into the cell. Alternatively, it is not clear if the insertion of a polynucleotide into a functional endogenous gene in the genome altering the endogenous the gene, would be encompassed by this claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Wheeler (US Patent 5,523,226).

Claim 1 is drawn to a non-murine mammalian pluripotent cell. Claims 2 and 3 encompass genetic modification of said cell wherein a gene is rendered non-functional or a functional gene is inserted. Wheeler discloses porcine ES cells (column 22 and claim 4). Wheeler teaches methods for introducing genes into the ES cells for production of a protein, and removing and/or altering a gene within the genome of the ES cell. Therefore, the claimed invention is anticipated.

The instant claims recite certain specific features, however all pluripontial ES cells are considered to inherently have the same features. As defined in the instant specification, a pluripotent ES cell is defined as 'a cell which can give rise to many differentiated cell types' and 'capable of self-renewal' (specification page 8; lines 6-12). Further, though a pluripotential cell is derived from primordial germ cells, it is not clear from the specification that the resultant product claimed herein would differ from the prior art product. This is similar to a product-by-process type limitation. Patentability of a product-by-process claim is determined by the novelty and

nonobviousness of the claimed product itself without consideration of the process for making it which is recited in the claims. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior was made by a different process (MPEP 2113 and *In re Thorpe*, 227 USPQ 964 (Fed. Cir. 1985)). Wheeler teaches a pluripotential non-murine cell and methods of culturing and maintaining said cultured cell indefinitely *in vitro*, methods demonstrating the production of a fully differentiated teratoma when injected into nude mice (column 14; lines 26-58), and that the normal karyotype of a euploid pig is 38 chromosomes (column 8; lines 12-20). Thus, the claims are anticipated. Therefore, for the reasons above and of record, the rejection is maintained.

Claims 1-4 rejected under 35 U.S.C. 102(b) as being anticipated by Pera *et al.* is withdrawn.

Applicants argue that the cells taught by Pera *et al.* are embryonal carcinoma (EC) cells, and that the post filing art of Wright (1998) and Sandberg *et al.* (1996) teach that pluripotent EC cells derived from a tetracarcinomas have abnormal chromosome complement. Though Examiner maintains that Pera *et al.* teach a putative human EC cell line and that EC cell lines can be cultured on feeder layers for 20 passages and are known to form embroid bodies, the post filing art clearly demonstrates that not all cells derived by this method maintain a normal karyotype. In light of the claim amendment and the failure of the art to teach a normal karyotype, the rejection is withdrawn.

Claims 1-3 stand rejected under 35 U.S.C. 102(b) as being anticipated by Norarianni *et al.*

Applicants argue that Wheeler (US Patent 5,523,226) and the post filing art of Hong *et al.* both teach that Norarianni *et al.* do not teach that a pluripotent non-murine embryonic stem cell was produced. Applicants arguments have been fully considered but not found persuasive.

Applicants arguments are directed to the embodiment of an embryonic stem cell which is totipotent (see Wheeler column 2; lines 60-64). Presently, the instant claims recite a non-murine pluripotential cell. Norarianni *et al.* teach pig embryonic pluripotent cells which were cultured on feeder layers and formed embroid bodies (pages 52 and 54). In light of the teachings of Norarianni *et al.*, the cells share characteristics with the instantly claimed cells prepared by the outlined process. Therefore, the claims are anticipated, and thus the rejection is maintained.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Woitach, whose telephone number is (703) 305-3732. The examiner can normally be reached on Monday through Friday from 8:00 to 4:30 (Eastern time).

If attempts to reach the examine by telephone are unsuccessful, the examiner's supervisor, Karen Hauda, can be reached on (703) 305-6608.

An inquiry of a general nature or relating to the status of the application should be directed to Kay Pickney whose telephone number is (703) 305-3553.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

Joseph T. Woitach

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